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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,191	08/24/2001	Hugh Redmond Brady	1377-0170P	9468

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EXAMINER
SULLIVAN, DANIEL M

ART UNIT	PAPER NUMBER
1636	13

DATE MAILED: 09/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,191	BRADY ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *8-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3,5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 24 August 2001 as the U.S. national stage of international application PCT/IE00/00026 filed 28 February 2000, which claims benefit of Irish patent application 990157 filed 26 February 1999. The preliminary amendments filed 19 December 2001 and 24 August 2001 have been entered.

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-7 and 11) and SEQ ID NO: 1 in Paper No. 12, filed 25 June 2003, is acknowledged. Applicant traverses the restriction to a single nucleic acid comprising one of the sequences set forth as SEQ ID NO: 1-6.

Applicant first points out that the Markush group is limited to only six sequences and is therefore sufficiently few in number that the entire claim can be searched and examined without serious burden. This argument has been fully considered but is not found persuasive. Each of the nucleic acid sequences of the Markush group represent a structurally and functionally unrelated chemical compound which would have to be searched and examined independently. Therefore, search and examination of each additional nucleic acid represents an additional burden. Furthermore, it is noted that, as this case is the national stage of an international application and therefore restricted under rules governing Unity of Invention, burden is not relevant to imposition of the restriction requirement.

Next, Applicant argues that all of the sequences share unity of invention as defined in M.P.E.P. §803.02. Applicant states, "all six sequences (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility". First, it must be pointed

out that Applicant is using the standard for unity of invention as it applies to U.S. restriction practice, not Unity of Invention before the International Searching Authority as is appropriate for applications filed under 35 U.S.C. §371. Furthermore, even under U.S. practice the restriction requirement is proper because the structural feature identified is not substantial. Applicant argues that all of the sequences share the common structural feature of being genes having a role in presentation of diabetic nephropathy. However, having a role in diabetic nephropathy is not a structural feature. It is a functional characteristic for which the disclosure provides no structural basis. Therefore, the only disclosed structural characteristic common to SEQ ID NO: 1-6 is that they are genes. Applicant asserts that the genes all have utility as a diagnostic marker or as a basis for identifying drugs useful for treatment of prevention of diabetic nephropathy. Clearly the fact that all of the sequences are genes is not a substantial structural feature because the vast majority of sequences sharing the structural feature of being a gene would not be useful as a diagnostic marker for diabetic nephropathy or as a basis for identifying drugs useful for treatment of prevention of diabetic nephropathy.

The requirement is still deemed proper and is therefore made FINAL.

Claims 8-10 and SEQ ID NO: 2-6 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Invention.

Specification

The disclosure is objected to because of the following informalities: The description of Figure 13 does not match the drawing. Specifically, the description provides no reference to the gel shown in the figure.

Appropriate correction is required.

Claim Objections

Claims 7 and 11 are objected to because of the following informalities: The claims are directed to nonelected subject matter (i.e., SEQ ID NO: 2-6). The nonelected sequences should be removed from the claims. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 11 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim is directed to a nucleic acid sequence which can be found in nature absent the hand of man and therefore encompasses non-statutory subject matter. Amending the claim to clearly indicate the hand of man in the claimed invention, such as by directing the claim to an isolated or purified nucleic acid, would be remedial.

Claim 11 is further rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well established utility.

The M.P.E.P. states, "[a] 'substantial utility' defines a 'real world' use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a 'real world' context of use are not substantial utilities" (2107.01(I)).

In the instant case, the elected invention is directed to a nucleic acid having the sequence set forth as SEQ ID NO: 1. The specification teaches that the nucleic acid has utility as a therapeutic target for drug development, as a diagnostic, and to generate knockout mouse models (see especially pages 12-13). The basis for these asserted utilities appears to be that expression of a gene comprising SEQ ID NO: 1 was identified as being differentially expressed in cultured mesangial cells exposed to elevated glucose concentrations.

It should first be pointed out that the Examiner could find no specific reference in the specification to SEQ ID NO: 1 as being a gene regulated by glucose. On page 18, the specification provides that SSH analysis suggested differential induction of 16 mRNAs in primary cultures of human mesangial cells. Of these 16, fifteen were confirmed to be differentially expressed by Northern analysis and are identified in Table 1. However, a gene comprising SEQ ID NO: 1 does not appear to be among the genes in Table 1 disclosed as differentially regulated in mesangial cells. Clearly, if the specification provides no evidence that the claimed nucleic acid is differentially expressed in mesangial cells exposed to elevated glucose, the skilled artisan would have to carry out further research to reasonably confirm that the claimed nucleic acid could be used for the purposes set forth in the specification, and therefore the asserted utility is not substantial.

The remainder of this rejection is set forth with the assumption that Applicant will be able to point to some evidence in the specification that a gene comprising SEQ ID NO: 1 is differentially expressed in mesangial cells exposed to elevated glucose. As indicated above, the asserted utility for the claimed nucleic acid is predicated on the nucleic acid having a role in the presentation of diabetic nephropathy. Assuming that the nucleic acid was identified in an assay

as set forth in the instant claim 1, the nucleic acid is either upregulated or downregulated in cultured mesangial cells as a consequence of altered glucose concentration. The art, exemplified by Murphy *et al.* (1999) *J. Biol. Chem.* 274:5830-5834 (made of record in the IDS filed 26 November 2003), teaches that the pathological hallmark of diabetic nephropathy is glomerulosclerosis due to accumulation of extracellular matrix and that propagation of mesangial cells under conditions of high ambient glucose has proved a useful *in vitro* model with which to probe the molecular basis for mesangial matrix accumulation. Thus, the art teaches that genes involved in accumulation of extracellular matrix might have utility as a therapeutic target for drug development, as a diagnostic, and to generate knockout mouse models for diabetic nephropathy. However, the art also teaches that many genes that are not involved in extracellular matrix formation are also regulated by glucose levels, such as genes involved in glycolysis and lipogenesis (see, for example, Girard *et al.* (1997) *Annu. Rev. Nutr.* 17:325-352; especially pages 329-332). Therefore, simply because a gene is differentially expressed "in the presence of a concentration of glucose sufficient to induce differential expression of a gene susceptible to such differential expression" (claim 1), does not mean that the gene has a role in the presentation of diabetic nephropathy. Given that the specification provides no direct evidence that the claimed nucleic acid plays a role in the presentation of diabetic nephropathy, the skilled artisan would have to carry out further research to reasonably confirm that the claimed nucleic acid could be used for the purposes set forth in the specification. Therefore the asserted utility is not substantial.

Claim 11 also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1-7 are indefinite in its recitation of "having a role in the presentation of diabetic nephropathy" in claim 1. The metes and bounds of "having a role" are not set forth in the specification and it is unclear what is required to meet this limitation. Must the gene actually contribute directly to the pathology of diabetic nephropathy in order to be considered as having a role? Or, would a gene that has some indirect relation to the presentation of diabetic nephropathy be encompassed? For example, does a gene that is required for energy production have a role in the presentation of diabetic nephropathy because it supplies energy for the production of extracellular matrix proteins? The claim should more clearly set forth what role the identified genes play in the presentation of diabetic nephropathy.

Claim 1 and method claims depending therefrom are additionally indefinite for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The claims are directed to a method for identifying a gene *having a role* in the presentation of diabetic nephropathy comprising the steps of culturing mesangial cells in a concentration of glucose that induces differential expression of glucose and identifying a gene so induced by suppression subtractive hybridization. However, the method steps set forth merely identify genes that are differentially expressed in mesangial cells in response to a given glucose concentration. For reasons set forth herein above under 35 U.S.C. §101 rejections, additional assays would have to be performed in order to establish that the genes identified actually have a role in the presentation of diabetic nephropathy. If applicant wishes to claim a method of identifying a gene having a role in the presentation of diabetic nephropathy, the method steps for the assays used to confirm said role in diabetic nephropathy must be clearly set forth. Alternatively, the method steps set forth are sufficient to identify a candidate, or a gene which might have a role in the presentation of diabetic nephropathy and amending the preamble according would overcome this rejection.

Claim 11 is indefinite in being directed to a sequence according to claim 7. As claim 7 is a method claim, it is unclear how the product of claim 11 is to be limited according to claim 7.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Murphy *et al.* (1998) *J. Am. Soc. Nephrol.* 9:637A.

Murphy *et al.* teaches a method for identifying a gene having a role in diabetic nephropathy comprising culturing mesangial cells in a medium in the presence of a concentration of glucose sufficient to induce differential expression of a gene and identifying the gene so induced by suppression subtractive hybridization. Thus, the teachings of Murphy *et al.* anticipate the limitations of claim 1. Murphy *et al.* further teach the method wherein the cells are cultured in a concentration of glucose sufficient to induce up-regulation according to claim 2, and the method wherein the concentration of glucose is greater than 5 mM according to the limitations of claim 3. The method of Murphy *et al.* is the same as the method disclosed in the instant application; therefore, the claims are anticipated by Murphy *et al.*

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms

JAMES KETTER
PRIMARY EXAMINER